**Citizen Petition to ban partially hydrogenated fat from the American Diet**
21 CFR 1030 Citizen Petition



The undersigned submits this petition under 21 CFR 1030 section of the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act. He requests to revoke the food labeling, trans fatty acids in nutrition labeling, *nutrition content* claims, and health claims. Docket No. 94P-0036.

**Section A: Action Requested**
I request to ban partially hydrogenated fat from the American diet.

**Section B: Statement of Grounds**

In the late 1800s, a French chemist discovered that an unsaturated fatty acid can be converted to a saturated fatty acid by bubbling hydrogen through a heated vegetable oil in a closed vessel. If completely hydrogenated, they become stearic acid. The commercial use of partially hydrogenation of oils began in the early 1900s. The exact fatty acid composition of the partially hydrogenated oil was essentially unknown until the development of gas chromatography (GC) by James and Martin in 1952. FDA, using the AOCS method, labeled the isomers in partially hydrogenated fat as only one peak (elaidic acid). It is only with a GC equipped with a 200 meter column that it is possible to further separate the fatty acid isomers of partially hydrogenated fat into at least 14 separate isomeric fatty acids [1, 2].

Using soybean oil as an example, differences between the natural oil and the result of the hydrogenation process is explained below. Soybean oil in its natural form [1] contains 52.5% linoleic (18:2 $\Delta^{9,12}$) acid, which is also known as 18:2n$^6$ or omega–6. It contains 7.5% linolenic (18:3 $\Delta^{9,12,15}$) acid also known as 18:3n$^3$ or omega-3. The designation 18:2 $\Delta^{9,12}$, and 18:3 $\Delta^{9,12,15}$ means that these two fatty acids have double bonds (points of unsaturation) at position 9 and 12 or 9,12 and 15 at which hydrogen can be added. During hydrogenation the double bond at any of these 9,12 or 9, 12, 15 positions can be shifted to form new cis and trans unsaturated fatty acid isomers not present in soybean oil. The double bond of the cis-natural linoleic and linolenic fatty acids can also change the configuration from cis to trans, creating a geometric isomer like trans $\Delta^{11}$-18:1 vaccenic acid in butter fat. Oleic acid, the largest percentage of the natural fatty acid in the human body, is cis $\Delta^9$-18:1 (the number after delta indicates the position of the double bond at the 18 carbon atom chain counting from the carboxyl group). Oleic acid goes through geometrical isomerisation during hydrogenation to trans $\Delta^9$-18:1 acid known as elaidic acid; thus the "natural" oleic acid is turned into elaidic acid during the hydrogenation process, and becomes

an "unnatural" fatty acid. It twists into a new form and can be both a cis and/or a trans fatty acid. In addition to geometrical isomerisation, the double bond of either cis or trans fatty acids can theoretically migrate along the 18 carbon chain of oleic, and linoleic acid changing their position from $\Delta^9$ or $\Delta^{9,12}$ creating five monoene cis positional isomers, 6 trans monoene isomers and 3 trans diene positional isomers [1]. Thus hydrogenated soybean oil contains 24.1% trans monoenes, 6.2% trans dienes and 9.4% cis monoene isomers or a total of 39.7% isomeric fatty acids. They were identified as cis and trans octadecenoic and octadecadienoic isomers on a GC equipped with a 200 meter column and by their mixed melting points with authentic octadecenoic and octadecadienoic acids purchased from Sigma Aldrich, St. Louis, MO. None of these fatty acids are present in natural soybean oil.

It was unknown until 1930 that linoleic (18:2 $n^6$) and linolenic (18:3 $n^3$) acids were essential fatty acids (EFA), and like the nine essential amino acids and the vitamins, cannot be synthesized in the human body; they must come from a diet that includes natural fats and oils. The 14 isomers in hydrogenated fat can be used as a source of energy but they cannot substitute for EFA because they do not have the required double bond structure.

EFA are required to synthesize the eicosanoids that are needed to regulate blood flow in the arteries and veins. Linoleic acid (n-6) is synthesized into arachidonic acid and linolenic acid (n-3) is synthesized into eicosapentaenoic acid. Both in turn are made into prostacyclin or thromboxane. Prostacyclins are synthesized in the endothelial cells that line the blood vessel wall. Thromboxanes are synthesized in the platelets in the blood. The balance between prostacyclin for flow and thromboxane for clotting is a very delicate one and can be changed by different diets and different drug prescriptions. Fish have already converted the linolenic acid they get from seaweed into eicosapentaenoic acid. Hence fish oil is often recommended as a dietary supplement. Prostacyclin and thromboxane can be made from linoleic acid as well. The least expensive source of omega-3 and omega-6 is soybean oil, which is sold as vegetable oil in a supermarket.

A study in 2004 [3], with piglets from mothers fed hydrogenated soybean oil showed that their arteries contained less linoleic acid converted to arachidonic acid than the arteries of piglets from mothers fed butterfat or corn oil. This indicated that the trans fat in hydrogenated soybean oil inhibited the metabolic conversion of linoleic to arachidonic acid. Furthermore, an analysis of

the fat embedded in the arteries of the piglets from mothers fed partially hydrogenated soybean oil showed that they contained 3% trans fat incorporated into their phospholipids by 48 days of age.

Vaccenic acid did not inhibit the metabolic conversion of linoleic to arachidonic acid. Epidemiological studies of intake of ruminant trans fat and risk of coronary heart disease (CHD) indicated that the intake of ruminant trans fatty acid was innocuous or even protective against CHD. Thus a study with an animal model has shown that trans-fat decreased synthesis of arachidonic acid from linoleic acid. This study [1] was carried a step further with endothelial cells those cells in the first layer of cells in the artery. They were cultured in a medium that contained the fatty acids of soybean oil or in a medium that contained the fatty acids of hydrogenated soybean oil. The latter cells contained trans-fat in their membrane phospholipid and significantly less arachidonic acid and secreted less prostacyclin than endothelial cells that had been cultured with the fatty acids from unhydrogenated soybean oil.

The ability to form prostacyclin from arachidonic acid was assayed using a radioimmunoassay kit. Trans-fat depressed the synthesis of prostacyclin. The addition of an excess amount of linoleic acid to this hydrogenated soybean oil fatty acids did not increase the secretion of prostacyclin in endothelial cells. The concentration of trans fatty acid rather than the concentration of linoleic acid was therefore responsible for regulating the synthesis and secretion of prostacyclin in endothelial cells. The trans fat in hydrogenated fat not only depressed the synthesis of prostacyclin that regulated the clotting of blood but also, could not serve as precursors for prostacyclin synthesis. The trans fat "incorporated" into the membrane lipids of blood vessels and muscle tissues and displaced the essential linoleic, linolenic and arachidonic acids [3].

I submitted an article to *Atherosclerosis, an international* journal in July 2008 entitled "the negative effects of hydrogenated fats and what to do about them." This article is now online and will be published in the August Issue of Atherosclerosis [2]. The editor requested that I include a mechanism for the cause of coronary heart disease (CHD).

Two mechanisms may be involved in CHD: one, the oxidation of the fatty acids and cholesterol in LDL leading to atherosclerosis [4] which is a process that occurs over a life time; two, the deposition of trans fat in the cardiovascular system of the veins and arteries which can

cause sudden death due to blockage. Trans fat calcifies both the arteries and veins and causes blood clots. Trans fat leads to the reduction of prostacyclin that is needed to prevent blood clots in the coronary arteries[1]. A blood clot in any of the coronary arteries can result in sudden death. The American Heart Association (AHA) has stated that 42% of victims of a sudden heart attack do not reach a hospital still alive.

We found that in the cells cultured with trans fat, the free arachidonic acid released by phospholipase action was shunted to metabolism by another pathway leaving less free arachidonic acid available as substrate for prostacyclin synthesis [3]. Cyclo-oxygenase (COX) is the enzyme that is necessary to make prostacyclin to keep the blood flowing, thus lowering the potential for a heart attack. Vane et al. have shown that COX is the enzyme that converts arachidonic acid to prostaglandin $H_2$, is further metabolized to prostanoids. Vane et. al. stated two isoforms of COX existed, a constitutive (COX-1) and an inducible (COX-2) enzyme. COX-2 may be the enzyme that recognizes the isomers produced during hydrogenation as a foreign substrate and reacts to them by causing inflammation and reduction of prostacyclin [5]. COX-2 is the inducible isoform of COX. COX-1 is present constitutively while COX-2 is expressed primarily after the inflammatory insult [6].

To demonstrate the process of calcification, endothelial cells cultured with/ without trans fat showed that trans fatty acid calcify arterial cells. One with a trans fatty acid added as the "unnatural" elaidic acid (t18:1 $n^9$) and the other with a cis fatty acid added as the "natural" oleic acid (cis 18:1 $n^9$) and testing with radioactive calcium. More radioactive calcium infiltration occurred into the endothelial cells cultured with elaidic acid than with oleic acid [7]. An autopsy of 24 human specimens showed that human subjects that had died of heart disease contained up to 12.2% trans fat in their adipose tissue, 14.4% in liver, 9.3% in heart tissue , and 8.8% in aortic tissue and in atheroma [8].

**Section C: Environmental Impact**

The following information is unfavorable to petitioner's position

The current mandate was stated on July 23, 2003. The FDA issued a directive that required labeling by January 1, 2006 of foods that contain trans (isomeric) fat [9]. The FDA based this directive on peer-reviewed articles. The FDA's major concern was the role of trans fat

in increasing the cholesterol concentration of low density lipoprotein (LDL). For simplicity isomeric fatty acids will be referred to as trans-fat.

Under the current mandate in the USA [9] food items with any amount of trans isomeric fatty acids are still allowed as long as they are labeled. Products containing less than 0.5 g/serving can be labeled as trans free. There was also no limit on how much hydrogenated fat food products can contain. In 2003, the daily intake of trans fat for men was estimated by the FDA to be nearly seven grams per day and for women almost five grams per day [9]. The FDA admitted the presence of hydrogenated fat in the diet would cause the deaths from heart disease of 500-1000 Americans/year at a cost of 1 billion dollars in medical costs [10].

In 2003, the metabolism of the trans fat in hydrogenated oil was assumed [9, 10] to follow the same pathway as the natural ruminant trans fat in butterfat. The FDA has stated [9] that the main reason for the trans fat in partially hydrogenated oil to remain in the diet in the USA rested on the generally held belief that trans fat is metabolized the same way as the natural trans (vaccenic acid) in butterfat. The FDA allowed the isomeric fatty acids in hydrogenated vegetable oils to remain in food products because they assumed that some of that trans fat may be from the natural vaccenic acid that has no harmful effects. Approximately 2.6% of the total daily fat intake is from trans fat and that 50% of the trans may be from vaccenic acid ($18:1n^{11}$).

The following information is favorable to petitioner's position.

Mozzafarian et. al. calculated the potential effect of reducing the intake of industrially produced trans fatty acids on the incidence of CHD in the United States. They predicted on the basis of changes in total and HDL cholesterol levels alone, a meaningful proportion of CHD events (3 to 6 percent) would be averted. However, they believed that this reduction was underestimated, since trans fats may also influence the risk of CHD through other mechanisms, such as inflammatory or endothelial effects. It has also been shown that trans fat inhibited the conversion of linoleic acid to arachidonic acid and inhibited the secretion of prostacyclin [1].

A computer search indicates that there are over ten thousand papers documenting the effects of trans fat on plasma lipid levels in the blood. The best known are the clinical studies by Katan and others in the 1990s that indicated trans fat increased LDL levels and lowered high-density lipoprotein (HDL) levels. An increase in LDL concentrations was believed to be a risk factor for CHD. They focused on the level of LDL and HDL levels in healthy subjects and found

that the replacement of 10% of energy from saturated fatty acids by trans fat decreased serum HDL by 21% and impaired flow mediated vasodilatation as an endpoint in dietary intervention. In view of the overwhelming amount of publications on trans fat, it is difficult to believe that trans fatty acid has any influence on blood clots.

If a mother is breast-feeding her child and also eating foods containing trans fat, she would have a substantial amount of trans fat in her milk supply and pass those to her infant. Pregnant porcine fed hydrogenated fat contained 11.3% trans fat in their milk at the birth of their piglets which decreased during lactation to 4% in 21 days [3]. The plasma of the piglets increased from 5% trans fat three days after birth to 15.3% at six weeks of age. Transferring this result to humans, a human mother would also transfer the trans fat in her milk supply to her infant. The infant would incorporate the trans fat into his/her arterial cells inhibiting arachidonic acid synthesis and prostacyclin secretion. Furthermore calcium deposition into the endothelial cells could be enhanced. To date, the FDA has not considered the daily intake of trans fat relevant to the health of small children since they do not exhibit overt heart disease. In cases where children have died of unknown causes and had been autopsied, 99% of them showed the beginning stages of hardening (calcifications) of the arteries, which ultimately can lead to heart disease.

The inflammatory process in the arteries is presently believed to be a risk factor in heart disease, and studies have shown that hydrogenated trans fat increases the inflammation in the arteries. We have shown that trans fatty acids are probably responsible for inflammation.

Epidemiological data collected by the Center for Disease Control (CDC) further illustrate the potential harmful effects of trans fat. These data showed that, death from CHD in the USA increased from 265.4/100,000 in 1900 to 581/100,000 population by 1950. During this time period, both margarine and shortening had a high percentage of trans fat (ranging from 39-50%) and a low percentage of linoleic acid (ranging from 6-11%) according to the technical director of the Institute of Shortening and Edible Oils. In 1968 Dr. Campbell Moses, medical director of the AHA, appointed a five member subcommittee on fats of the AHA nutrition committee to revise the 1961 version of "Diet and Heart Disease." As a member of this subcommittee I urged Dr. Moses to ask the President of the Institute of Shortening and Edible Oils Inc to have its member organizations decrease the amount of trans fatty acids and increase the amount of EFA in their shortenings and margarines. At the time it was known that an increase in EFA composition of a

dietary fat would lower plasma cholesterol levels and there was strong evidence that trans fatty acids increased plasma cholesterol levels. The first revised version by the AHA committee stated:

"Partial hydrogenation of polyunsaturated fats results in the formation of trans forms which are less effective than cis, cis forms in lowering cholesterol concentrations. It should be noted that many currently available shortenings and margarines are partially hydrogenated and many contain little polyunsaturated fat of the natural cis, cis form." The members of the Institute of Shortening and Edible Oils Inc objected to this version. The second revised and distributed version, omitted references to hydrogenated fat and cis fatty acids stated:

"Margarines that are high in polyunsaturates usually can be identified by the listings of a liquid oil" first among the ingredients. Margarines and shortenings that are heavily hydrogenated or contain coconut oil, which is quite saturated, are ineffective in lowering the serum cholesterol." The industry agreed to lower the trans fatty acids and increase the level of EFA in shortenings and margarine. Dr. R.I. Levy, director of the National Heart, Lung, and Blood Institute at the time, believed 1968 a watershed, as the incidence of CHD has steadily declined in the US since 1968. Why it decreased remained unknown in 1968. (11)

On October 24th, 1978, ten years after the reformulation of hydrogenated fat, the National Institute of Health (NIH) held a conference in Bethesda, Maryland, on the Decline in CHD Mortality. A recent editorial in Circulation cited this symposium. Three major conclusions reached were; 1) The decrease in CHD mortality was real and not a result of artifacts or changes in death certificate coding, 2) Both primary prevention through changes in risk factor fundamentals and clinical research leading to better medical care probably have contributed to but did not fully explain the decline, and 3) A precise quantification of the causes requires further studies." In hindsight, the reformulation of hydrogenated fat with its lowering of the trans fatty acids and raising of linoleic acid could have also been responsible for the decline. The per capita consumption of hydrogenated fat continued to increase after 1950. However, the increase in the linoleic acid content in the reformatted 1968 fat and the increasing use of soybean oil in salad dressing and other food items could have helped to keep a decreasing death rate from CHD. The death rate from heart disease dropped substantially during the next decades even

though the consumption of hydrogenated fat kept increasing and animal fat was decreasing [11]. Lower trans fat and increased linoleic acid are possible explanations for this change.

The death rate from CHD declined after 1968 from 588.8/100,000 to 217/100,000 in 2004 in the USA. According to AHA data, 451,300 Americans died of CHD in 2004. Heart disease is still the number one cause of death. However, in a population of approximately 300 million, today the deaths would have been 1,480,000 at the 1950 rate according to the National Institute of Health (NIH) [12]. A recent study based on the autopsy of young men [13] showed the CHD rate has been increasing since 2004. The recent reformulation of hydrogenated fat raises the trans fatty acid levels from 20% to almost 40% [1].

**Section E: Certification**

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which is unfavorable to the petition.

Fred A. Kummerow

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